

REMARKS**Rejection of Claims and Traversal Thereof**

In the April 29, 2008 Office Action:

1. Claims 1, 4-10, 12-15 18 and 23 were rejected under 35 USC §112,second paragraph;
2. Claims 1, 5, 9, 10, 12 and 13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vo-Dinh (U.S. Patent No 5,814,516, hereinafter Vo-Dinh), as evidenced by Lakowicz (U.S. Patent Application No. 2002/0160400, hereinafter Lakowicz 1); Doukas et al., (Proceedings of the National Academy of Science (1984) 81,4790-4794, hereinafter Doukas) and Letuta et al., (Quantum Electronics (2001) 31 (10): 925-928, hereinafter Letuta) in further view of Qi et al. (Applied and Environmental Microbiology (2001) 67(8) 3720-3277, hereinafter Qi); and
3. Claims 1, 4-10, 12-16 and 18-27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cao, et al., (Nanoparticles within Raman Spectroscopic Fingerprints for DNA and RNA Detection, Science, Aug 2002, Vol. 297, pp 1536-1540, hereinafter Cao); as evidenced by Malicka,et al., (Biopolymers (2003) 72(2) 96-104, hereinafter Malicka) and Lukomska et al., (Biopolymers and Biophysical Research Communication (2005) 328: 78-84) in view of Lakowicz 1, and in further view of Lakowicz, (Radiative Decay Engineering: Biophysical and Biomedical Applications,” Analytical Biochemistry, 2001, Vol. 298, pp 1-24, hereinafter Lakowicz 2).

These rejections are hereby traversed and reconsideration of patentability of the pending claims is therefore requested in light of the following remarks.

Rejections under 35 USC §112,second paragraph

Applicants have amended the claims according to the suggestions of the Office and thereby obviating this rejection. Withdrawal is requested.

Rejections under 35 U.S.C. 103 (a)

Claims 1, 5, 9, 10, 12 and 13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vo-Dinh, as evidenced by Lakowicz 1, Doukas and Letuta in further view of Qi. Applicants submit that the proposed combination does not in any way establish a *prima facie* case of obviousness.

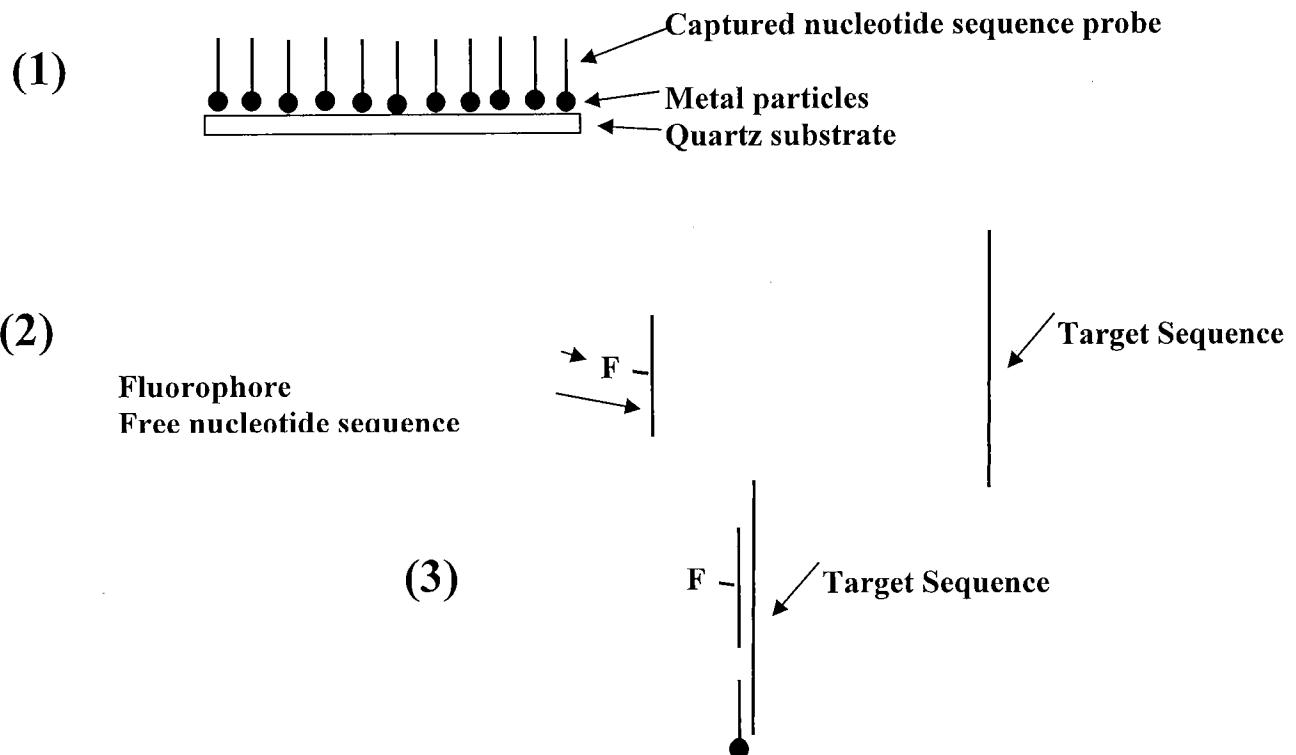
The Office mistakenly believes that Vo-Dinh describes all the limitations of claim 1 excepting the placement of the fluorophore near metallic particles. Applicants vigorously disagree because neither Vo-Dinh alone or in combination with Lakowicz 1 teaches the components of the presently claimed invention.

Applicants' claimed invention as recited in claim 1 include:

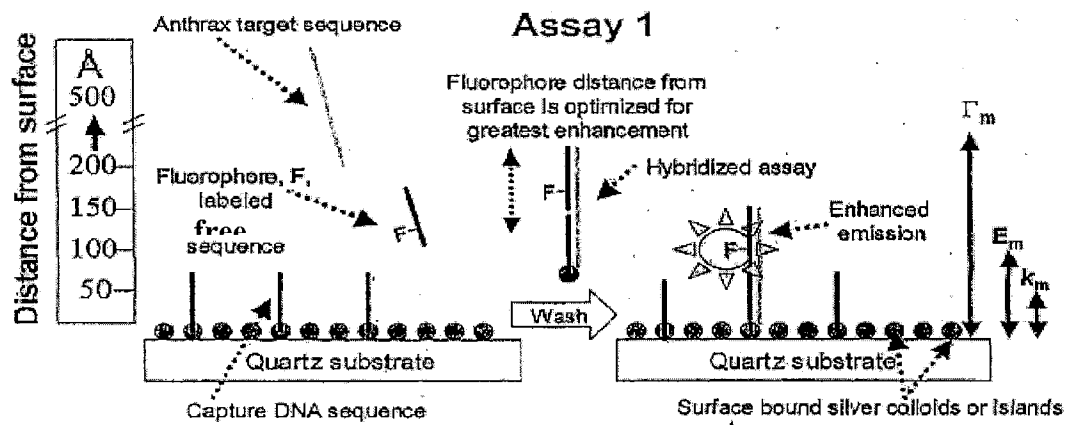
(1) a substrate with immobilized metal particles with a captured nucleotide sequence probe complementary to a first portion of a nucleotide sequence of the *B. anthracis*; and

(2) a free nucleotide sequence probe, wherein the free nucleotide sequence probe has an affinity for a second portion of the nucleotide sequence of *B. anthracis* and has attached thereto a fluorophore,

(3) both of these two probes are necessary to determine if a test sample includes the nucleotide sequence of *B. anthracis*.



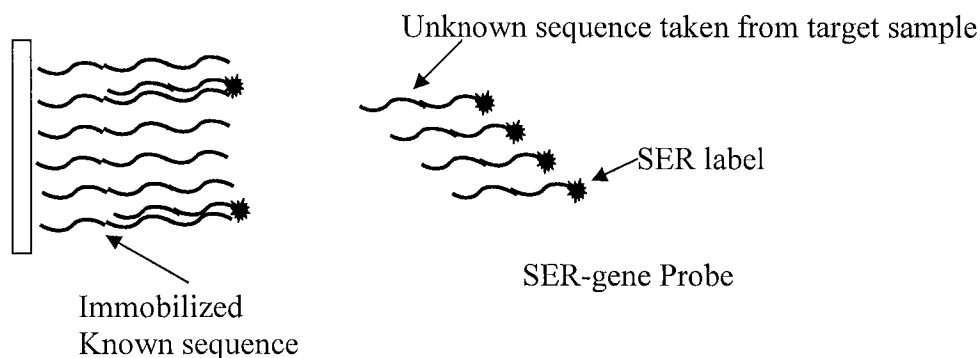
It should be very clear that the nucleotide sequence of *B. anthracis* is known so the two probes include sequences that are complementary to two different regions of the known anthrax sequence and are prepared to attach to different regions of the *B. anthracis* sequence. Clearly if there is no *B. anthracis* sequence in the sample then the captured nucleotide sequence probe will remain unbound, and thus, the free probe will not bind to anything and in turn—no signal. In the alternative, if there is *B. anthracis* sequence in the sample then it will attach to the captured nucleotide sequence probe and then the free nucleotide sequence probe will bind to the second site that is complementary to the free nucleotide sequence probe and a signal produced. Thus applicants' system includes the use of two separate and distinct probe sequences (a captured and free nucleotide sequence) that are complementary to different sections of the target nucleotide sequence. The free nucleotide probe sequence includes a fluorophore positioned a distance from the metal surface. This is shown below by applicant's Figure 1.



Importantly, the use of the two probes that have affinity for different sequence residues in the target sequence is advantageous because it allows for increased sensitivity. Thus, when both probes are bound to the target sequence there is very little doubt regarding the identity of the bound sequence. In fact using the two probes provides for additional verification that the target sequence is indeed anthrax.

The Office makes reference to several sections of the Vo-Dinh reference and specifically column 3 and column 7 in an attempt to show that the Vo-Dinh system is similar to applicants' claimed system. However, the text considered by the Office does not in any way teach all the required components. The reference discusses several methods of use but all the methods use only include two sequences for hybridization. For example column 3 teaches a system for preparing SER-gene probes wherein the SER-gene probes includes an unknown sequence taken from a sample suspected of containing the target

nucleotide strands and an SER label bound thereto, wherein the SER label can be unique to that unknown sequence. The SER probe genes containing the unknown sequences are contacted with immobilized oligonucleotide strands of known sequences that are adsorbed on a sampling medium wherein the immobilized oligonucleotide strands are complementary to the target oligonucleotide strands, if in the sample. Incubating the SER gene probe solution with the sampling medium for the SER gene probes to contact the immobilized oligonucleotide strands and sufficient enough as for hybridization to occur, thereby producing hybridized oligonucleotide material. Thus, the system included the following



This embodiment is further discussed in column 7, lines 45 to 48, wherein an SER active surface comprises an oligonucleotide strand of known sequence immobilized on the SERS active substrate which later hybridizes to the SERS labeled target oligonucleotide strand of unknown sequence. This section of the Vo-Dinh is recreated below:

“alter” the adsorptivity of the roughened surface. The oligonucleotide material immobilized on the roughened surface of the SERS active substrate comprises either the labeled SER gene probe immobilized on the SERS active substrate which later hybridizes with the target oligonucleotide strand before analysis or it comprises an oligonucleotide strand of known sequence immobilized on the SERS active substrate which later hybridizes to the SERS labeled target oligonucleotide strand of unknown sequence.

Clearly as discussed in column 6, the Vo-Dinh method is used for testing samples to see if they contain a target sequence, such as, from a virus. The Vo-Dinh method includes an immobilized known sequence on a substrate and then takes an unknown sequence from a test sample that may include sequences from the virus and labeling same with a SEC label. If and when a labeled unknown sequence hybridizes with the known sequence, the probe will provide an indication of the binding. However, it is very clear that

this system includes only 2 sequences (1) an unknown sequence and (2) the known sequence. There are not two probes that bind to different sequences of a target sequence such as applicants' claimed invention, and as such, Vo Dinh does not provide the additional benefit of verification that the sequence is indeed the target sequence. The applicant should not have to remind the Office that there are many levels of affinity between sequences, and the Vo-Dinh method does not provide such assurance that the sequence is indeed the target sequence.

The other system used by the Vo-Dinh reference includes the systems as set forth below and described in Figures 2 and 6 of Vo-Dinh, however neither system discloses, teaches or suggests the presently claimed invention. Figure 2 shows a probe 6 with a label that attaches to sequence 4 while Figure 6 shows that the labeled sequence is immobilized. Further, there are only two sequences. Clearly by viewing these systems, it is evident that neither describes the assay system of the present invention as shown above.

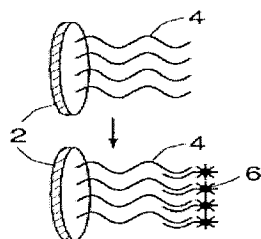


Figure 2

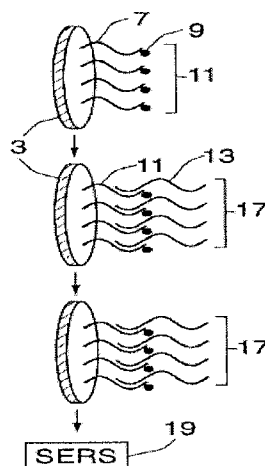


Figure 6A

According to the Examiner the SEC-label is inherently positioned the correct distance from the metallic surface of Vo-Dinh as evidenced by Lakowicz 1. However, even with the combination of Vo-Dinh and Lakowicz 1, all the limitations of the presently claimed invention are not disclosed or suggested.

Initially, it should be noted that Lakowicz 1 does not teach or suggest the system of the present invention. Lakowicz teaches only the use of two sequences

Initially, it should be noted that Lakowicz 1 provides for metallic islands on quartz plates but Vo-Dinh teaches a **continuous layer** of metallic material that is then covered with a polymeric type or oxide type coating that **must be roughened** to be acceptable for use. There is **nothing** in Vo-Dinh that teaches the

use of unexposed metallic particles. One skilled in the art would never consider taking the metallic islands that include a smooth surface of Lakowicz 1 and using same in the Vo-Dinh system because it is very evident that the Vo-Dinh system would no longer operate as intended or it could change the mode of operations. According to the court in *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification and the Office has not established a *prima facie* case of obviousness.

The Office has cited several other references in an attempt to establish a *prima facie* case of obviousness, however the addition of Doukas, Letuta and/or Qi does not rectify the shortcomings of the Vo-Dinh and Lakowicz 1 combination. If none of the prior art teaches or suggests all the claimed components then the prior art does not defeat the patentability of claims 1, 5, 9, 10, 12 and 13. Applicants request the withdrawal of this rejection under section 103.

3. Claims 1, 4-10, 12-16 and 18-27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cao as evidenced by Malicka and Lukomska in view of Lakowicz 1 and 2. Once again applicants insist that the proposed combination does not defeat the patentability of the presently claimed invention.

Initially, it should be noted that applicants' application has a priority date of November 26, 2002 and to establish a *prima facie* case of obviousness, the cited prior art has to be available to the skilled artisan at the time of filing. Thus any prior art cited has to be available before the November 26, 2002. Clearly, the Malicka reference with a date of 2003 (*Biopolymers* (2003) 72(2) 96-104) and the Lukomska reference with a date of 2005 (*Biopolymers and Biophysical Research Communication* (2005) 328: 78-84) do not meet this requirement. As such, applicants are not even considering them in this response because neither reference is competent prior art.

According to the Office, Cao is a primary reference and when combined with a multiplicity of other references teaches the presently claimed invention. This Cao reference published on August 30, 2002 and applicants have an effective filing date of November 26, 2002 (provisional application) which is clearly within a one year period of the Cao publication. Thus, it is evident that applicants have the right to swear behind this reference. As such, applicants submit herewith is a Declaration under executed by Dr. Geddes who was the author of Exhibit 1 filed herewith and found in Appendix A. The Declaration attests to facts showing completion and possession of the claimed invention prior to the publication date of Cao reference.

Reference	Effective Date
Cao	August 30, 2002

The Declaration includes appended Exhibit 1.

Exhibit 1 is a copy of power point slide having a date of creation and modification, that have been blackened out, prior to the August 30, 2002 publication date of the Cao reference. Exhibit 1 clearly shows the use of the claimed assays of the present invention wherein the two nucleotide probes are used to bind with a target sequence of anthrax.

Exhibit 1 in addition to the enclosed Declaration provides evidence of completion and possession of the method and assay to isolate anthrax of the instant claimed invention prior to the effective date of the Cao reference. As such, applicants request that the Cao reference be removed as a competent reference.

The Office has also cited the two Lakowicz references, that being, both Lakowicz 1 and Lakowicz 2.

The present application has a filing date of November 26, 2003 with a priority and effective filing date of November 26, 2002. The Lakowicz 2 reference U.S. Patent No. 7,095,502 issued on August 22, 2006 was originally filed on August 5, 2003. As such the Lakowicz 2 reference would be considered to meet the time requirements of a 102(e) reference and was commonly owned by the University of Maryland, Baltimore and University of Maryland Biotechnology Institute, at the time of filing of the present application. Consistent with the provisions of MPEP §706.02(I)(2), the statement hereinabove by applicants disqualifies U.S. Patent No. 7,095,502 from being used in a rejection under 35 U.S.C. §103(a) against claims of the present application. See also, MPEP §§ 706(I)(1).

Accordingly, because the Lakowicz 2 reference has been disqualified, it is evident that the only remaining reference Lakowicz 1 is not sufficient to establish a *prima facie* case of obviousness.

In light of the foregoing discussion and the fact that all of claimed limitations are not disclose it is clear that the Office has not met its burden of establishing a *prima facie* case of obviousness.

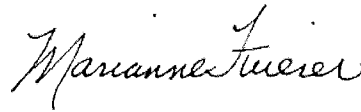
Petition for Extension and Fees Payable

Applicants petition for a one month extension extending the deadline for filing a response from July 29, 2008 to August 29, 2008 with a fee due of \$60.00 to be paid electronically with the filing of this response. If any additional fee is found due for entry of this amendment, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Bertagna reconsider the patentability of the pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. If any issues remain outstanding incident to the allowance of the application, Examiner Bertagna is requested to contact the undersigned attorney at (919) 286-8089.

Respectfully submitted,

A handwritten signature in cursive script, reading "Marianne Fuierer".

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APPENDIX A